Clinico-pathological conference

HIV-associated dilated cardiomyopathy

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Case Report *(Dr R F Miller)*
The patient was a 39 year old male homosexual book publisher. He first presented to this hospital in December 1988 with a diagnosis of oral hairy leukoplakia and at the time was found to be HIV 1 antibody positive and to be hepatitis B immune. Not long after this he developed a cough, increasing exertional dyspnoea and a reduced exercise tolerance. He was admitted for investigation in January 1989. A chest radiograph showed bilateral infiltrates and he was mildly hypoxaemic. *Pneumocystis carinii* was seen on Grocott's staining of bronchoalveolar lavage fluid. The patient made a good recovery on treatment with nebulised pentamidine given once daily for 21 days using a Respirgard II nebuliser. He then began treatment with zidovudine and commenced secondary prophylaxis with monthly inhaled pentamidine. He did not attend regularly for his pentamidine prophylaxis. He remained well apart from developing oropharyngeal candidiasis which responded to treatment with oral fluconazole.

He was admitted as an emergency in April 1989 with a toxic confusional state. On examination he was markedly dyspnoeic and again mildly hypoxaemic. A sample of sputum induced by inhalation of hypertonic saline revealed *Pneumocystis carinii*. He was treated with intravenous co-trimoxazole and on this regime his confusional state and blood gases rapidly improved. He developed a diffuse macular rash after ten days of this therapy and completed treatment for the pneumonia with intravenous pentamidine for ten days. He subsequently recommenced monthly inhaled pentamidine prophylaxis and attended regularly for this. When seen in the outpatients clinic he reported subjective memory loss and also some episodes of confusion which were short lived. Despite these symptoms he was continuing to work full-time and continued to do so over the next 16 months.

In October 1990 he was again admitted as an emergency. He had just returned from holiday in Spain and had become confused and incoherent and then had three grand mal fits. On examination he had generalised hypertonia and hyperflexia. He was unconscious with no focal neurological signs; he responded to pain purposefully. Fundoscopy was unremarkable. General examination failed to detect any cause for his symptoms. Initially the chest radiograph and arterial blood gases were normal, over the 24 hours following admission the patient became pyrexial (temperature = 41·5°C) and also dyspnoeic and tachypnoeic with a respiratory rate of 44 breaths per minute. Coarse crackles were audible in both lung bases. A repeat chest radiograph showed patchy consolidation in both lower lobes and he was hypoxaemic, with a PaO_2 of 7·3 kPa (breathing 60% oxygen via a face mask). Fibreoptic bronchoscopy and bronchoalveolar lavage failed to detect *Pneumocystis carinii* or any other pathogen. CT of the head revealed cortical atrophy only; lumbar puncture revealed a protein of 1·1 g/l, a CSF glucose of 4·3 mmol/l (with a simultaneous blood glucose of 7·8 mmol/l). No cells were seen in the CSF and cryptococcal antigen and Indian Ink stain were negative. Toxoplasma serology on both CSF and serum was negative as was syphilis serology and culture for cytomegalovirus and *Herpes simplex* virus. An EEG showed non-specific abnormalities consistent with a post-ictal state. The patient was given phenytoin to prevent further fits and was commenced on intravenous broad-spectrum antibiotics as he was thought to have an aspiration pneumonia. He made a steady recovery and was subsequently discharged home taking zidovudine, phenytoin and resuming prophylactic inhaled pentamidine.

In February 1991 he was admitted with a two week history of cough productive of small quantities of mucopurulent sputum. In addition, he was feeling rather more tired than usual, had night sweats and an intermittent fever. Culture of a sputum sample and also of faeces grew *Salmonella enteritidis*. He was admitted for further assessment. On examination he

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had lost a considerable amount of weight, in the chest there were coarse bi-basal crackles but otherwise there were no other abnormalities. The haemoglobin was 7·5 g/dl and the white count was $3·5 \times 10^9$ (75% neutrophils). He was given a blood transfusion and was initially treated with oral amoxycillin; further sputum samples obtained whilst taking this antibiotic continued to be positive for *Salmonella enteritidis*. Treatment was therefore changed to oral ciprofloxacin and he was allowed home to complete the course of treatment.

He was re-admitted after only ten days at home. He reported episodes of dysphasia with paraesthesia of his right hand and foot and difficulty controlling his right hand. He had experienced several of these episodes, each lasting several minutes. In addition, he reported a mild generalised headache but had no nausea or vomiting and denied photophobia. On examination he looked well with no neck stiffness; fundoscopy was normal. There were no lateralising signs in the nervous system and the cranial nerves were intact. In the cardiovascular system his blood pressure was 120/180 mm Hg, the pulse was regular at 80 per minute and auscultation of the heart was unremarkable. Investigations at this stage included cerebral CT which again demonstrated cortical atrophy with no space occupying lesions. Lumbar puncture showed a CSF protein of 0·6 g/l and glucose of 2·6 mmol/l (simultaneous blood glucose 5 mmol/l). Other investigations included normal urea and electrolytes, but his liver function tests had become abnormal with an alkaline phosphatase enzyme level of 1694 (normal < 280) iu/l, an AST of 752 (normal < 50) iu/l with a normal bilirubin. Culture of the CSF was negative and cryptococcal antigen was again negative. Psychometric testing revealed some evidence of short term memory loss and an EEG again showed non-specific changes with no evidence of epileptiform activity. An autoantibody screen was negative as was a test for anticardiolipin antibody; lupus anticoagulant was not detected.

Five days after admission to hospital, whilst undergoing investigations, the patient acutely deteriorated becoming pyrexial, tachypnoeic with a respiratory rate of 35 per minute and tachycardic with a pulse rate of 140 per minute. He was also hypotensive, blood pressure = 85/70 and auscultation of the heart revealed a third heart sound. In the chest there were fine basal end-inspiratory crackles. Arterial blood gases taken whilst the patient was breathing 60% oxygen revealed a PaO_2 of 9·9 kPa. An ECG (fig 1) was abnormal showing widespread ST segment and T wave changes, especially in the inferolateral leads. A chest radiograph (fig 2a) showed bilateral interstitial shadowing and there was a rather globular appearance to the heart. Culture of sputum and blood revealed *Salmonella enteritidis*. It was not clear whether the patient had developed left ventricular failure or had a further episode of *Pneumocystis carinii* pneumonia. He was treated with intravenous co-trimoxazole given in small volumes of dextrose and also given intravenous frusemide. Despite these manoeuvres his chest radiograph deteriorated (fig 2b) showing worsening interstitial infiltrates and his blood gases also worsened, the PO_2 falling to 7·8 kPa whilst breathing 60% oxygen. The patient was transferred to the intensive care unit for

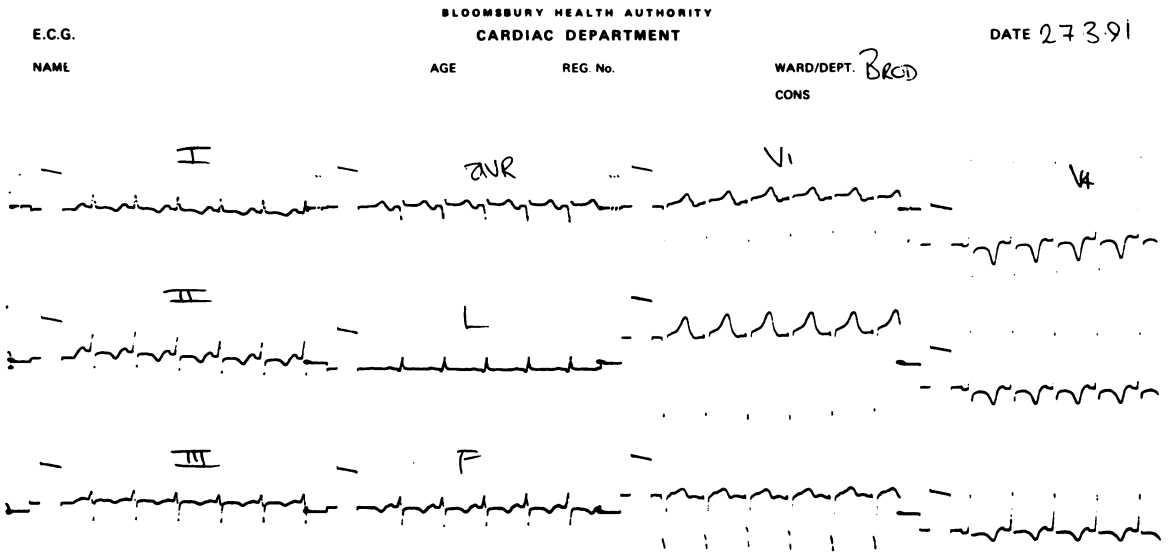
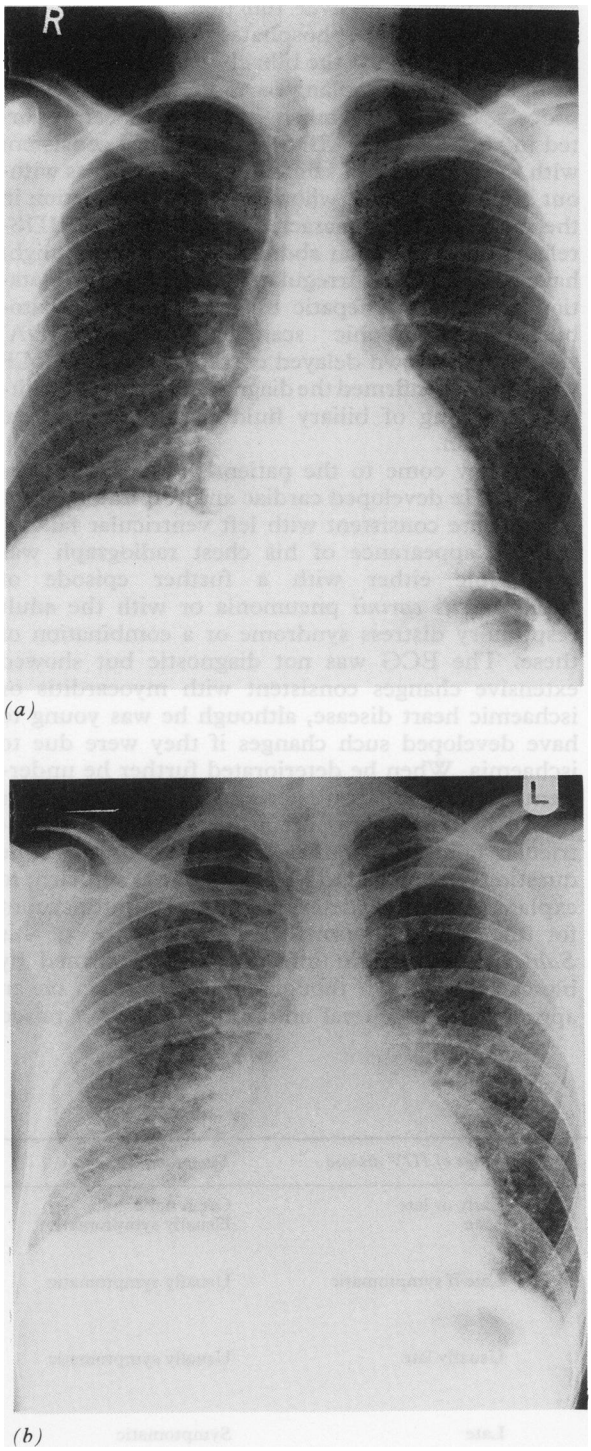


Fig 1 ECG showing sinus tachycardia and widespread ST and T wave changes, especially inferolaterally.



(a)

(b)

Fig 2 Chest radiographs: (a) At the time of the patient's acute deterioration, showing bilateral interstitial shadowing: the heart has a rather globular shape. (b) Just prior to transfer to the intensive care unit showing more pronounced interstitial shadowing.

further monitoring. A right heart catheterisation was carried out using a Swan Ganz catheter. The right atrial pressure was 4 mmHg which was normal and the mean pulmonary capillary wedge pressure (an indirect measure of left atrial pressure) was also normal at 8 mmHg; the systemic vascular resistance was reduced and the cardiac output was raised at 10 l/min (normal = 2·5–7 l/min). These data strongly suggested that the patient did not have left ventricular failure as the cause of his deterioration; the values were compatible with septicaemia. Blood cultures continued to grow *Salmonella enteritidis* and so intravenous ciprafloxacin was commenced. Despite correcting the hypoxaemia with continuous positive airways pressure (CPAP) ventilation via a face mask, the patient became hypotensive and anuric. Terminally he refused further treatment and died peacefully.

Discussion *(Dr R Gilson)*

This man presented with *Pneumocystis carinii* pneumonia as his AIDS-defining diagnosis in January 1989. Following treatment with inhaled pentamidine he had a further episode of pneumocystis pneumonia within 3 months. It is impossible to distinguish here between a failure of treatment leading to an early relapse and a failure of prophylaxis after adequate treatment. His poor compliance with pentamidine prophylaxis may favour the latter, emphasising the need to monitor compliance. In either event he was successfully treated with parenteral therapy.

In October 1990 he presented with a confusional state which had been an additional feature of his earlier presentation with recurrent *Pneumocystis carinii* pneumonia. In October he also had generalised fits which were complicated by aspiration pneumonia. There were no focal neurological signs. Investigations to reveal a possible opportunistic infection or tumour were inconclusive. The only abnormality was cortical atrophy detected by CT. MRI, which is a more sensitive examination, was not performed. In the absence of evidence of any other pathology, the diagnosis was presumably HIV encephalopathy. Convulsions are a recognised feature of this syndrome which is also associated with a reduced threshold for the development of an acute confusional state which may complicate any septicaemic episode.

In February 1991 he presented with mild respiratory and constitutional symptoms which were associated with disseminated salmonellosis. Gastrointestinal symptoms are often absent in HIV-infected patients with *Salmonella enteritidis* infection. Characteristically the presentation is sub-acute with fever and constitutional symptoms. This patient was also anaemic which could have been due to his

zidovudine therapy but a rapid decline in haemoglobin after a prolonged period of treatment (here nearly 2 years) would favour another cause such as bone-marrow infiltration or, as here, septicaemia. In retrospect, although further down the list of differential diagnoses, bacterial endocarditis might also have been considered even without cardiac signs.

After failing to clear the sputum of *Salmonella enteritidis* with amoxycillin his treatment was changed to ciprofloxacin. With hindsight he was allowed home too soon. It was already known that his compliance with pneumocystis prophylaxis was poor, he was subject to episodes of confusion and had also complained of poor memory. Poor compliance with treatment during this period may be relevant to his later deterioration. His readmission 10 days after discharge was because of neurological symptoms. Unlike the earlier episodes, he had episodic focal symptoms on the right side with paraesthesia, dyspraxia and dysphasia. He alo described headache and photophobia. In spite of the history he had no focal signs and CT was unhelpful. There was no evidence of meningitis. There was perhaps an even stronger case for MRI to be performed on this admission. MRI may detect evidence of cerebral toxoplasmosis or lymphoma at an earlier stage than CT, or may detect multiple lesions when CT detects only one. It is also more sensitive in detecting the white matter abnormalities characteristic of progressive multifocal leucoencephalopathy. The possiblity of a vasculitis or embolic disease was investigated with tests for auto-antibodies but none was found. Anti-cardiolipin antibodies have been associated with focal neurological deficits in patients with AIDS. There were no abnormal cardiac signs; however, an ECG and echocardiogram might have excluded a cardiac cause such as endocarditis with more confidence. He had no further neurological symptoms.

Abnormalities of liver function tests were then noted. The alkaline phosphatase value was greater than the AST, while the bilirubin was normal. This would suggest a cholangitis rather than a hepatic process. Salmonella cholangitis has not been reported in patients with AIDS but would be consistent with the pathology of salmonellosis in patients without HIV infection in whom presence of infection in the gall-bladder is characteristic. If he had AIDS-related cholangitis, an abdominal ultrasound might have demonstrated irregular thickening and dilatation of the extra-hepatic biliary ducts. A hepatobiliary scintigraphic scan (technetium-HIDA) would have shown delayed excretion and an ERCP would have confirmed the diagnosis as well as permitting sampling of biliary fluid for microbiological examination.

We now come to the patient's final precipitous decline. He developed cardiac and respiratory signs which were consistent with left ventricular failure, but the appearance of his chest radiograph was compatible either with a further episode of *Pneumocystis carinii* pneumonia or with the adult respiratory distress syndrome or a combination of these. The ECG was not diagnostic but showed extensive changes consistent with myocarditis or ischaemic heart disease, although he was young to have developed such changes if they were due to ischaemia. When he deteriorated further he underwent right heart catheterisation. The pressures recorded did not support a diagnosis of left ventricular failure but rather one of septicaemia. The question remained as to whether this was sufficient to explain such a rapid deterioration and how to account for the ECG abnormalities. Persistence of his *Salmonella enteritidis* infection was confirmed by blood culture even though he was by then on an appropriate parenteral antibiotic. Despite a raised

Table Cardiac disease in HIV infection

Clinical syndrome	*Aetiology*	*Stage of HIV disease*	*Symptoms*
Pericardial effusion	Unknown	Early or late	Often none
	TB	Late	Usually symptomatic
	OI Kaposi's sarcoma		
Dilated cardiomyopathy	HIV	Late if symptomatic	Usually symptomatic
	OI Drug misuse		
	Unknown		
Non-dilated cardiomyopathy	Kaposi's sarcoma	Usually late	Usually symptomatic
	Non-Hodgkin's lymphoma		
	OI		
	Unknown		
Ventricular dysrhythmias	HIV	Late	Symptomatic
	OI Drugs (such as pentamidine)		
Non-infectious thrombotic endocarditis	Unknown	Late	Usually asymptomatic
	Fungi e.g. *Aspergillus fumigatus*		

Key: TB = *Myobacterium tuberculosis*; OI = opportunistic infections.

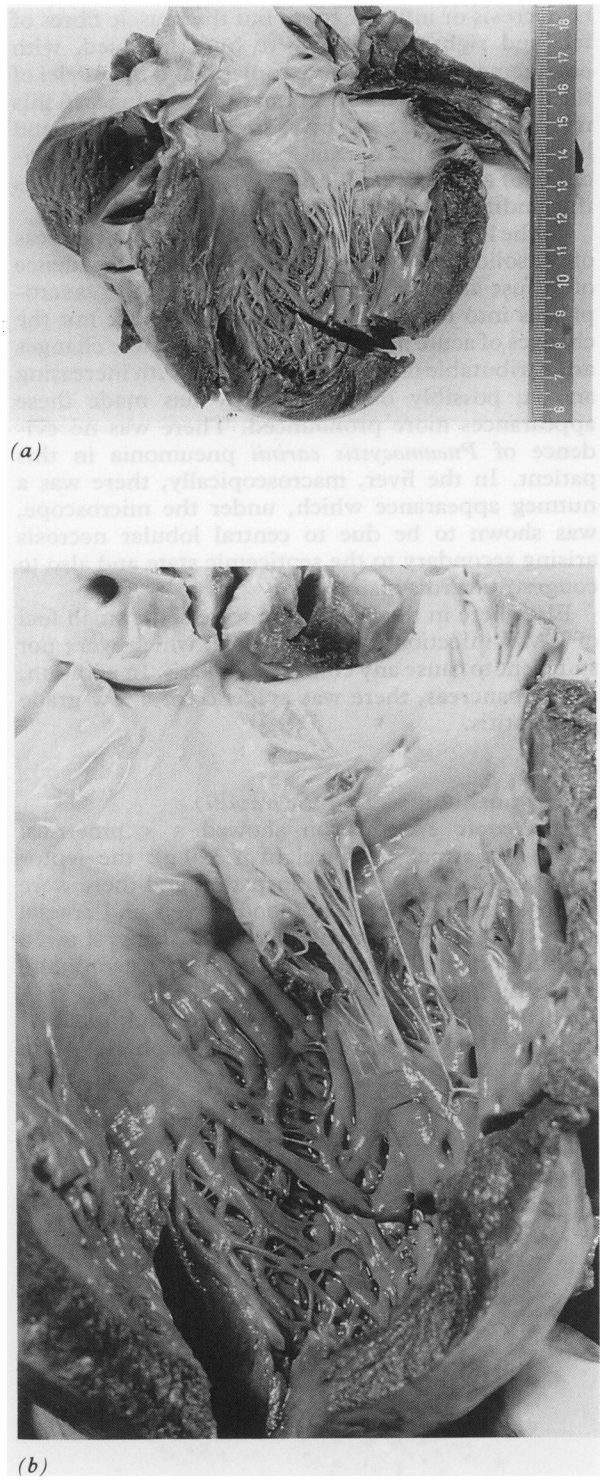


Fig 3 (a) Heart opened up to expose mitral valve, left ventricle and aortic valve. The cavity of the left ventricle is dilated. (b) Closer view of the left ventricle to show hypertrophy of the wall of the left ventricular myocardium.

cardiac output intially he became hypotensive and anuric. This all suggests that he did have a cardiac disorder in addition to the septicaemia. Evidence for this might have been obtained if an echocardiogram had been performed when he was transferred to the intensive care unit.

Early post-mortem studies of cardiac lesions in patients with AIDS suggested that they rarely had clinical significance.[1] Cardiac involvement in HIV disease is now recognised as an important cause of morbidity in 5–10% cases and mortality in 1–5%.[2] Its importance may increase further with improved survival due to antiretroviral therapy and better control of opportunistic infections. The clinical syndromes encountered in HIV-associated cardiac disease include pericardial effusion, dilated or non-dilated cardiomyopathy, ventricular dysrhythmias and non-infectious thrombotic endocarditis (table). Data on the prevalence of the different syndromes are still limited and often biased by the method of study, particularly in post-mortem series.[3 4] Few studies have included sufficient numbers of patients with early HIV infection. One study from the UK of a population of 115 patients found echocardiographic evidence of cardiomyopathy in 18·6% of cases.[5] Although most cases occurred in patients with advanced HIV disease, isolated left or right ventricular dilation occurred earlier, but was found only in drug users, which may suggest aetiologies other than HIV.

In a review, Anderson and Virmani[2] reported that 25% of patients with HIV-infection but without cardiac symnptoms had a pericardial effusion. Symptomatic effusion may be a complication of tuberculosis or, in later disease, of opportunistic infection or Kaposi's sarcoma.[6] Dilated cardiomyopathy is usually a late manifestation, symptomatic, and may be associated with opportunistic infection or septicaemia.[7] In most cases, however, the aetiology remains uncertain and may be a direct effect of HIV.[7–10] Even when an opportunistic organism such as *Toxoplasma gondii* is identified histologically, there may be little evidence of an inflammatory response to support a causative association. In those cases without other identified infections, the cardiomyopathy may be characterised by myocyte necrosis with a variable amount of inflammatory infiltrate or a lymphocytic infiltrate without necrosis.[11] Apart from HIV, other putative aetiologies include nutritional deficiencies (depressed selenium levels) and the catabolic state of end-stage disease.[2]

Non-dilated cardiomyopathy is less common; it may be due to infiltration by Kaposi's sarcoma or lymphoma and may be fatal. Ventricular dysrhythmia and "sudden death" of presumed cardiac origin has been associated with opportunisitic infection, drugs and lymphoma, but evidence of myocarditis without other predisposing cause has been seen and may affect the conducting system.[2]

In conclusion, cardiac involvement in advanced HIV disease is now well recognised as a cause of morbidity and mortality. The clinical course in this case is compatible with the clinical syndrome of HIV-assocated cardiomyopathy.

Clinical diagnoses

1 *Salmonella enteritidis* septicaemia
2 Cardiomyopathy – secondary to HIV infection?
– secondary to salmonella infection?
3 HIV encephalopathy

Pathology *(Professor L Michaels and Dr C Hage)*

At necropsy the body was that of an emaciated caucasian man. There were no lesions of Kaposi's sarcoma on the skin or palate. On opening the chest there were bilateral pleural effusions containing straw coloured fluid, about a litre on each side. In addition, in the abdomen there was approximately 700 ml of ascitic fluid which was also straw-coloured. The most striking feature at necropsy was the enlargement of the heart, which weighed 500 g (normal = 330 g), the enlargement being mainly left ventricular. The visceral pericardium was smooth and there was very little in the way of pericardial effusion. On opening the heart the most striking abnormality was a combination of left ventricular dilatation together with hypertrophy of the ventricular wall (fig 3). The ventricle was actually dilated to twice its normal volume. Both the mitral and aortic valves were healthy and there was no evidence of endocarditis. The coronary arteries were normal and there were no foci of previous myocardial infarction. On the right side of the heart there was again hypertrophy and dilatation of the right ventricle. The tricuspid and pulmonary valves were normal. Microscopically (fig 4) there was no evidence of myocarditis, with no areas of necrosis or inflammation, but the muscle fibres of left and right ventricle were hypertrophied, with enlargement of both the sarcoplasm and the nuclei of the muscle fibres. So in summary, the changes in this man's heart were of biventricular dilatation and hypertrophy with normal heart valves and no evidence of an acute focal lesion. The term that best fits this finding is dilated cardiomyopathy.

In the lung, there was diffuse oedema but no areas of consolidation. Microscopically there was evidence of diffuse alveolar damage with extrusion of macrophages into the alveolar lumina. These are not the changes of acute heart failure. Many of these changes are attributable to his terminal illness with increasing anoxia; possibly oxygen therapy has made these appearances more pronounced. There was no evidence of *Pneumocystis carinii* pneumonia in this patient. In the liver, macroscopically, there was a nutmeg appearance which, under the microscope, was shown to be due to central lobular necrosis arising secondary to the septicemic state and also to congestive cardiac failure.

Elsewhere in the body there were some small foci of CMV infection in the adrenals, which were not sufficient to cause any clinical problems. In addition, in the pancreas, there was evidence of a low grade pancreatitis.

Neuropathology *(Dr F Scaravilli)*

Macroscopic examination showed a symmetrical brain of normal size (weight 1 330 g); the leptomeninges were thin and transparent and there were no focal lesions. Cerebral blood vessels and cranial nerves appeared normal. Coronal slices showed markedly dilated ventricles; cortex, subjacent white matter and deep grey nuclei appeared normal.

Histological examination revealed multiple discrete foci of lymphoma in the hemispheric white

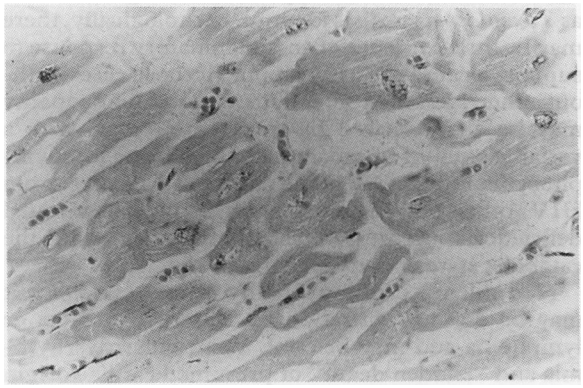


Fig 4 Myocardial fibres of left ventricle showing enlarged nuclei and sarcoplasm. Note lipofuscin granules in the vicinity of the nucleus in most cells. (H & E × 400).

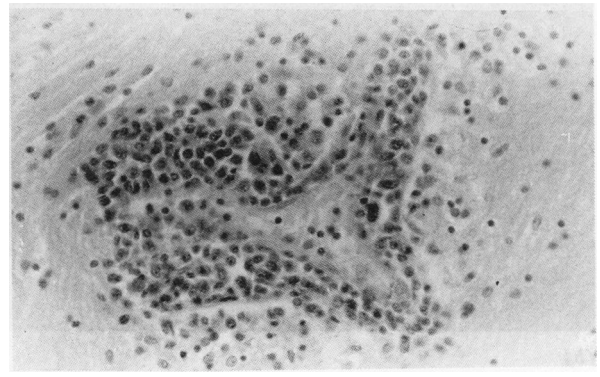


Fig 5 Photomicrograph of the hemispheric white matter showing a perivascular focus of lymphoma. Some tumour cells can also be seen to infiltrate the adjacent white matter. (H & E × 300).

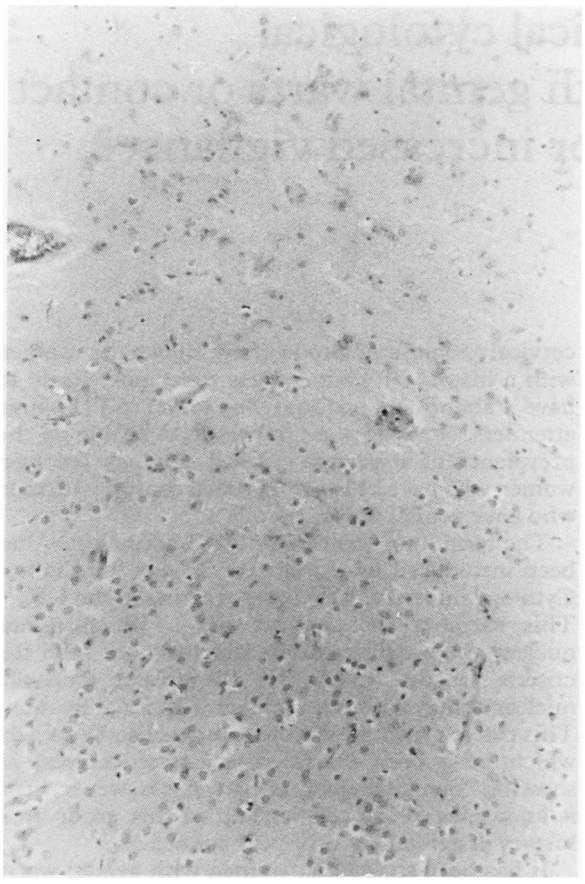


Fig 6 Photomicrograph of the cortical grey matter. Astrocytes appear increased in number and size. Some of them have two nuclei. (H & E × 120).

matter, particularly in the subependymal regions of the lateral ventricles. The aggregates of tumour cells were almost exclusively perivascular (fig 5) and consisted of medium to large size cells with hyperchromatic, in places indented, nuclei and variable amounts of cytoplasm. Mitotic figures were seen. The cortical grey matter, which was exempt from lymphomatous infiltration, showed diffuse glial hyperplasia (fig 6). Some of the astrocytes appeared considerably enlarged with abundant cytoplasm and one or two vesicular nuclei. These changes may well have been present for several weeks or even a month or so and may have accounted for some of the patient's neurological problems prior to death. The lymphoma that was present in the brain may also have contributed to his neurological status.

Professor L Michaels

There was no evidence of lymphoma in the rest of the body.

Pathological diagnosis

1 Dilated cardiomyopathy – HIV associated
2 Cerebral lymphoma
3 Diffuse cerbral gliosis

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